REMARKS

The Claim Amendments

Claims 76-79 and 94-96 have been amended to advance prosecution of this application. Applicants' cancellation of any subject matter from the claims, which is not to be interpreted as acquiescence to any outstanding rejection, is without prejudice or waiver of their right to pursue that subject matter in an application claiming priority herefrom under 35 U.S.C. § 120.

The claim amendments are discussed more fully below, in response to the Examiner's remarks as a result of examination.

The Obviousness-Type Double Patenting Rejection

The Examiner also maintained the rejection of claims 76 to 102 under the judicially created doctrine of obviousness-type double patenting as being "unpatentable" over claims 1 to 10 of United States Patent No. 5,503,976. Upon indication of allowable claims in this application, applicants stand ready to file a Terminal Disclaimer.

The Rejections Under 35 U.S.C. § 112, First Paragraph - "Maintained Rejections"

Claims 76-79 and 82-102 stand rejected under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one of skill in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Specifically, the Examiner further contends:

> "that the claims, as written, encompass polynucleotides and methods for using polynucleotides that vary substantially in length and in nucleotide composition, including polynucleotides containing genomic DNA that have not been taught or described in the specification."

The Examiner also suggests that "(1) since the specification has only described three specific DR-beta sequences and because the genus of sequences encompassed by the recitation in the claims is large with no common structural feature, other than amino acids 38-45 . . . the three species described in the specification are not representative of the broadly claimed genus," and "(2) the prior art does provide compensatory structural or correlative teachings that would enable the skilled artisan to identify or predict the nucleotide composition of the large number of sequences encompassed for use in the methods."

Applicants disagree. However, in an effort to advance the prosecution of this application, applicants have amended the claims to delete the sub-part of claims 76-79 and 94-96, which recited the language "allelic variants of any of the foregoing DNA sequences." Those claims as now written, are directed to the processes and kits that contain DNA sequences that are capable of hybridizing to the polymorphic DNA regions encoded by amino acids

8-14, 26-32 and 72-78 of the HLA-DR-β chain locus, and complementary sequences thereof.

The Examiner further asserts that:

> " . . . the claims are drawn to a method using DNA sequences which are capable of hybridizing to polymorphic sequences which makes the genus of DNA sequences which can be used in the method even larger. The large genus of sequences identified by the broad scope of 'hybridization' (ie. large range of hybridization conditions) would not at all predictably have the same structural characteristics as the disclosed species because there is no way to determine what variations would be tolerated without making the method inoperable as a typing method. Further, the specification provides no teaching or description as to which positions within the regions taught in the specification, including the conserved region, can be altered or varied such that the regions are still characteristic of HLA-DR-B alleles."

The Examiner also asserts that:

> "[b]ecause the specification does not teach or describe such variations or how such variations would correlate specifically for typing methods, ie. variants characteristic of DRB1, DRB3, DRB4, or DRB5 alleles which were later identified, the fact that they may [be] isolated using the sequences disclosed does not set forth a description of the DNA itself."

Applicants disagree with both of these assertions for the following reasons.

Applicants point out that the official comments to the Written Description Guidelines emphasize that "describing the complete chemical structure, i.e., the DNA sequence, of a claimed DNA is one method of satisfying the written description

requirement, but it is not the only method", and "there is no basis for a per se rule requiring disclosure of complete DNA sequences or limiting DNA claims to only the sequences disclosed." 66 Fed. Reg. at 1101. Rather, another way of fulfilling the written description requirement is by disclosing sufficiently detailed, relevant identifying characteristics to provide evidence that the applicants were in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed function and structure, or some combination of such characteristics. 66 Fed. Reg. at 1101.

The Examiner's contentions are without merit, particularly when viewed in light of the Declaration of Dr. Jack L. Strominger, a pioneer in the field of HLA antigens, filed on May 16, 2002 and Dr. Strominger's supplemental declaration filed concurrently herewith.

In Dr. Strominger's Second Declaration, he states:

> " . . . with the three polymorphic HLA-DR-β sequences and one conserved HLA-DR-β sequence, in hand, a person skilled in the art of HLA-DR-β typing would have understood that the designated "polymorphism" of the three disclosed HLA-DR-β DNA sequences provided the "common structural feature" by which the nucleotide sequences of additional polymorphic regions, namely 8-14, 26-32, and 72-78 of the HLA-DRB1 locus could be obtained."

With respect to the Examiner's reliance on The Regents of the University of California v. Eli Lilly Company, 43 USPQ2d 1225 (Fed. Cir. 1995) ("Lilly"), the facts of this application may be clearly distinguished from the facts of Lilly. Specifically, in Lilly the decision of the court that only the nucleic acid species described in the specification (i.e., nucleic acids encoding rat insulin) met the description requirement does not apply to the sequences of applicants' claims for two reasons. First, all of applicants' sequences are from the same species, and in fact are alleles of the same species of gene (i.e, human HLA-DR-β). By contrast, Lilly involved an attempt to broaden the scope of the disclosure to encompass an entire genus, based on a single disclosed species. There is a marked distinction between the number and types of sequences which are encompassed by a genus, as opposed to alleles of a single species. Second, as described above, Dr. Strominger has provided expert testimony which states that the DNA sequences taught by applicants in fact provided enough "structural detail" to identify additional HLA-DR-β alleles. In particular, Dr. Strominger states in ¶ 17 of his earlier May 16, 2002 declaration:

> " . . . [b]ecause the '786 application taught three regions of polymorphism (which are known today to be present in almost all of the HLA-DR-B1, HLA-DR-B3, HLA-DR-B4, and

> HLA-DR-B5 alleles identified and sequenced as of January 2002), a person of skill in the art at July 30, 1982 would have been able to use these three polymorphic regions in combination with then-routine DNA hybridization techniques to distinguish and categorize newly identified HLA-DR-β chain alleles, while using the conserved DNA sequence, encoding amino acids ("aa") 39-45 to distinguish non-HLA-DR-β chain sequences. That conserved sequence would bind specifically at the 39-45 aa region of HLA-DR-β chain alleles other than the HLA-DR-β-A, HLA-DR-β-B and HLA-DR-β-C alleles described in the '786 application."

Dr. Strominger goes on to state at ¶ 22 of his May 16, 2002 declaration:

> "[t]he '786 application first identified and characterized polymorphic and conserved regions which proved to hold a structural and functional similarity shared among various HLA-DR-β chain alleles. Such similarity, in turn, provided information sufficient to allow a person of skill in the art, as of July 30, 1982, to identify HLA-DR-β chain alleles, other than the HLA-DR-β-A, HLA-DR-β-B and HLA-DR-β-C alleles exemplified in the '786 application, as well as DNA sequences capable of hybridizing to any one of those polymorphic regions of such other HLA-DR-β chain alleles."

Dr. Strominger's expert testimony confirms that applicants' disclosure of a single conserved region of HLA-DR-β and three polymorphic regions of HLA-DR-β provided a predictability of structure which reasonably conveyed to one of skill in the art at the time that the inventors were in possession of the claimed invention. Such disclosure satisfies the written description requirement:

> "predictability of the structure of a species can be premised on (1) whether the level of skill in the art leads to a predictability of structure; and/or (2) whether teachings in the application or prior art lead to a predictability of structure." The Written Description Guidelines, Section II.A.

With respect to the Examiner's reliance on Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111), Fiers v. Revel (25 USPQ2d 1601), and Fiddes v. Baird (30 USPQ2d 1481), for the same reasons detailed above for Lilly, the propositions set forth in these decisions are distinguishable based on the fact that the underlying facts are different - i.e., the present application does not seek to claim multiple species of genes, rather , the claims are directed exclusively to polymorphic DNA sequences of the "human" HLA-DR-B1 genes. In fact, in an effort to advance prosecution, applicants have even removed the previously claimed element of "allelic variants" of said "human" HLA-DR-B1 genes.

The Rejections Under 35 U.S.C. § 112, First Paragraph - "New Grounds of Rejections"

Claims 76-79 and 82-102 stand rejected under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to which it pertain, or with which it is most nearly connected, to make and/or use the invention."

Specifically, the Examiner suggests that "the claims, as written, encompass polynucleotides and methods of using polynucleotides that vary substantially in length and in nucleotide composition." (see page 15, lines 5-7 of the December 17, 2002 Office Action). More particularly, the Examiner asserts that "the three sequences described in the specification [are] do not enable the skilled artisan to make or use the broad scope of the claimed invention without undue experimentation." (see page 15, lines 10-12 of the December 17, 2002 Office Action) Applicants disagree.

Testifying as to the skill of the art at applicants' effective filing date, Dr. Strominger states that:

> "the '786 application identifies and characterizes three specific polymorphic regions (i.e., amino acids 8-14, 26-32 and 72-78) and one specific conserved region (i.e., amino acids 39-45) and DNA sequences encoding those regions from three specific HLA-DR-β chain alleles (i.e., HLA-DR-β-A, HLA-DR-β-B and HLA-DR-β-C). Based on that teaching, it is my opinion that a person of skill in the art as of July 30, 1982, would appreciate common features for identifying HLA-DR-β chain alleles, other than HLA-DR-β-A, HLA-DR-β-B and HLA-DR-β-C alleles, and DNA sequences capable of hybridizing to a polymorphic region selected from amino acids 8-14, 26-32 or 72-78 of such other HLA-DR-β chain alleles." (Strominger Decl. ¶ 12, dated May 16, 2002).

Additionally, Dr. Strominger explains that, as a person of skill in the art as of July 30, 1982, it would have been

possible for him to use the conserved and polymorphic DNA sequences disclosed in the '786 application to identify other HLA-DR-β alleles. (Strominger Decl. ¶ 17, dated May 16, 2002). In essence, Dr. Strominger believes that applicants' identification of amino acid regions 8-14, 26-32 or 72-78 of HLA-DR-β–A, -B, and -C as "polymorphic regions" of HLA-DR-β, provided a common structural feature, which, when combined with applicants' identification of amino acid regions 39-45 of HLA-DR-β–A, -B, and -C as "conserved regions" of HLA-DR-β, provided structural features characteristic of, and allowing identification of, additional HLA-DR-β alleles, in turn allowing identification of DNA sequences capable of hybridizing to those polymorphic regions of those additional HLA-DR-β alleles, for use in HLA-typing. (Strominger Decl. ¶¶ 13-14, dated May 16, 2002).

Dr. Strominger reiterates in his supplemental declaration that:

> "with the three polymorphic HLA-DR-β sequences and one conserved HLA-DR-β sequence, in hand, a person skilled in the art of HLA-DR-β typing would have understood that the designated 'polymorphism' of the three disclosed HLA-DR-β DNA sequences provided the 'common structural feature' by which the nucleotide sequences of additional polymorphic regions, namely 8-14, 26-32, and 72-78 of the HLA-DRB1 locus could be obtained. (Second Strominger Decl. ¶ 6, filed concurrently herewith)

Additionally, Dr. Strominger testifies that:

> "[a]s a person of skill in the art, as of July 30, 1982, it is my opinion that the polymorphic nature of the nucleotide sequence located at the 8-14, 26-32 and 72-78 regions of the HLA-DR-β allele would in fact provide useful structural information, for the identification and characterization of the nucleotide sequence located at the 8-14, 26-32 and 72-78 regions of other HLA-DR alleles." (Second Strominger Decl. ¶ 7, filed concurrently herewith)

The Examiner also contends that "the specification has not taught which positions within the regions specifically disclosed can be changed and still be HLA-DR beta alleles and useful in a typing method."

Dr. Strominger addresses this specific point by testifying that:

> "it is my belief that a person of skill in the art, as of July 30, 1982, would recognize that 'any' nucleotide change within the polymorphic regions that did not result in a gross change in the structure of the HLA-DR-β chain would be tolerated, and thus useful in a HLA typing method. By contrast only 'minimal' nucleotide changes would be tolerated within the conserved region defined in the application." (Second Strominger Decl. ¶ 9, filed concurrently herewith)

Dr. Strominger goes on to detail the reasons why the Examiner is incorrect in her assertion stating:

> "[f]or example, of presently identified HLA-DR-β1, only 4 alleles vary at position 45 (G->R), 1 allele varies at position 39 (R->H), and 2 alleles vary at position 40 (F->Y). (see Exhibit K, submitted with my declaration dated May 16, 2002). All of these amino acid changes are the result of a 'single' nucleotide change, located at the end or adjacent to the end of the nucleotide sequence encoding the conserved region of the HLA-DR-β allele. Accordingly, there is no doubt in my mind that the nucleotides encoding the conserved region (e.g. amino acids 39-45), as described in

> the '786 application would in fact hybridize to 'all' of the presently identified HLA-DR-β alleles. Additionally, of the seven alleles that contain a minor sequence variation, nearly all of the alleles represent rare subtypes (e.g., B1*0433; B1*0823 - last two numbers represent the subtype of each allele, high numbers are rare), and in some cases represent a single individual. Thus, these noted minor variation would represent a 'very minor' faction of the entire population. It is my opinion that these minor variations would not diminish the importance and usefulness of the conserved region in the method and typing kits described in the '786 application." (Second Strominger Decl. ¶ 9, filed concurrently herewith)

Finally, the Examiner asserts the specification "has not taught the variations within the DRB4 alleles which were later identified (for example within the conserved region of amino acids 39-45), such that the skilled artisan would have known at the time of filing that such variations would still be DR-beta alleles." Applicants disagree.

Applicants point to ¶ 10 of the Second Strominger Declaration (filed concurrently herewith), which explains that this point (i.e., the variations within the DRB4 alleles) is irrelevant in practice because typing is never carried out for the HLA-DRB3, HLA-DRB4 or HLA-DRB5 alleles. More particularly, applicants reiterate that the HLA-DRB3, HLA-DRB4 or HLA-DRB5 alleles are encoded at loci that are distinct from the DRB1 locus and the genes expressed at these loci are minor HLA sequences of no importance in typing of HLA genes that are expressed at the

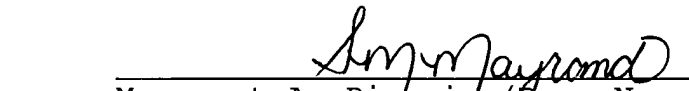
HLA-DRB1 locus, which is the focus of this claims in this application.

For all of the foregoing reasons, the § 112, first paragraph rejection of claims 76-79 and 82-102 should be withdrawn.

Applicants request that the Examiner consider the foregoing amendments and remarks and pass this application to issue.

Should the Examiner believe an interview to be of use to the end, applicants' representatives stand ready to schedule an interview at the Examiner's convenience.

Respectfully submitted,



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APPENDIX

76. (Amended) An HLA-DR typing process comprising the steps of:

(a) hybridizing DNA in a sample to be typed to a DNA sequence, said DNA sequence being capable of hybridizing to a polymorphic region of an HLA-DR-β chain locus of the human lymphocyte antigen complex to allow determination of one or more HLA-DR alleles, said polymorphic region being encoded by a DNA sequence selected from the group consisting of:

(i) DNA sequences encoding amino acids 8-14 of said locus;

(ii) DNA sequences encoding amino acids 26-32 of said locus;

(iii) DNA sequences encoding amino acids 72-78 of said locus;

[(iv) DNA sequences which are allelic variants of any of the foregoing DNA sequences;] and

(iv) DNA sequences which are fully complementary to any of the foregoing DNA sequences, and

(b) detecting areas of hybridization between said DNA in said sample and said DNA sequence.

77. (Amended) An HLA-DR typing process comprising the steps of:

(a) restricting a first DNA isolated from an individual to be typed with at least one restriction endonuclease;

(b) size-fractionating said restricted DNA;

(c) hybridizing said size-fractionated DNA to be typed to a second DNA, said second DNA being capable of hybridizing to a polymorphic region of an HLA-DR-β chain locus of the human lymphocyte antigen complex to allow determination of one or more HLA-DR alleles, said polymorphic region being encoded by a DNA sequence selected from the group consisting of:

(i) DNA sequences encoding amino acids 8-14 of said locus;

(ii) DNA sequences encoding amino acids 26-32 of said locus;

(iii) DNA sequences encoding amino acids 72-78 of said locus;

[(iv) DNA sequences which are allelic variants of any of the foregoing DNA sequences;] and

(iv) DNA sequences which are fully complementary to any of the foregoing DNA sequences, and

(d) detecting areas of hybridization between said size-fractionated DNA and said second DNA.

78. (Twice Amended) An HLA-DR typing process comprising the steps of:

(a) hybridizing DNA in a sample to be typed to a DNA sequence, said DNA sequence being capable of hybridizing to a polymorphic region of an HLA-DR-β chain locus of the human lymphocyte antigen complex to allow determination of one or more HLA-DR alleles, said polymorphic region being encoded by a DNA sequence selected from the group consisting of:

(i) DNA sequences encoding a majority of the amino acid sequence of amino acids 8-14, 26-32 or 72-78 of a polypeptide sequence coded for by DNA insert DR-β-A, DR-β-B or DR-β-C;

[(ii) DNA sequences which are allelic variants of any of the foregoing DNA sequences;] and

(ii[i]) DNA sequences which are fully complementary to any of the foregoing sequences, and

(b) detecting areas of hybridization between said DNA in said sample and said DNA sequence.

79. (Twice Amended) An HLA-DR typing process comprising the steps of:

(a) restricting a first DNA isolated from an individual to be typed with at least one restriction endonuclease;

(b) size-fractionating said restricted DNA;

(c) hybridizing said size-fractionated DNA to be typed to a second DNA, said second DNA being capable of hybridizing to a polymorphic region of an HLA-DR-β chain locus of the human lymphocyte antigen complex to allow determination of one or more HLA-DR alleles, said polymorphic region being encoded by a DNA sequence selected from the group consisting of:

(i) DNA sequences encoding a majority of the amino acid sequence of amino acids 8-14, 26-32 or 72-78 of a polypeptide sequence coded for by DNA insert DR-β-A, DR-β-B or DR-β-C;

[(ii) DNA sequences which are allelic variants of any of the foregoing DNA sequences;] and

(ii[i]) DNA sequences which are fully complementary to any of the foregoing sequences, and

(d) detecting areas of hybridization between said size-fractionated DNA and said second DNA.

94. (Amended) An HLA-DR typing kit comprising a DNA sequence selected from the group consisting of:

(i) DNA sequences encoding amino acids 8-14 of an HLA-DR-β chain locus of the human lymphocyte antigen complex;

(ii) DNA sequences encoding amino acids 26-32 of an HLA-DR-β chain locus of the human lymphocyte antigen complex;

(iii) DNA sequences encoding amino acids 72-78 of an HLA-DR-β chain locus of the human lymphocyte antigen complex;

[(iv) DNA sequences which are allelic variants of any of the foregoing DNA sequences]; and

(iv) DNA sequences which are fully complementary to any of the foregoing DNA sequences.

95. (Amended) An HLA-DR typing kit comprising a DNA sequence which hybridizes to an HLA-DR-β chain locus of the human lymphocyte antigen complex, said DNA sequence being capable of hybridizing to a polymorphic region of said locus to allow determination of one or more HLA alleles for use in HLA-DR-β typing, said polymorphic region being encoded by a DNA sequence selected from the group consisting of:

(i) DNA sequences encoding amino acids 8-14 of said locus;

(ii) DNA sequences encoding amino acids 26-32 of said locus;

(iii) DNA sequences encoding amino acids 72-78 of said locus;

[(iv) DNA sequences which are allelic variants of any of the foregoing DNA sequences]; and

(iv) DNA sequences which are fully complementary to any of the foregoing DNA sequences.

96. (Amended) An HLA-DR typing kit comprising a DNA sequence which hybridizes to an HLA-DR-β chain locus of the human lymphocyte antigen complex, said DNA sequence being capable of hybridizing to a polymorphic region of said locus to allow determination of one or more HLA alleles for use in HLA-DR-β typing, said polymorphic region being encoded by a DNA sequence selected from the group consisting of:

(i) DNA sequences encoding a majority of the amino acid sequence in a region consisting essentially of amino acids 8-14, 26-32 or 72-78 of a polypeptide sequence coded for by DNA insert DR-β-A, DR-β-B or DR-β-C;

[(ii) DNA sequences which are allelic variants of any of the foregoing DNA sequences]; and

(ii[i]) DNA sequences which are fully complementary to any of the foregoing sequences.